Journal of Alzheimer's Disease 40 (2014) 37–43
DOI 10.3233/JAD-131841
IOS Press

Short Communication

No Differences in Hippocampal Volume between Carriers and Non-Carriers of the ApoE ε4 and ε2 Alleles in Young Healthy Adolescents

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ISSN 1387-2877/14/$27.50

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Accepted 28 October 2013

Abstract. Alleles of the apolipoprotein E (ApoE) gene are known to modulate the genetic risk for developing late-onset Alzheimer's disease (AD) and have been associated with hippocampal volume differences in AD. However, the effect of these alleles on hippocampal volume in younger subjects has yet to be clearly established. Using a large cohort of more than 1,400 adolescents, this study found no hippocampal volume or hippocampal asymmetry differences between carriers and non-carriers of the ApoE ε4 or ε2 alleles, nor dose-dependent effects of either allele, suggesting that regionally specific effects of these polymorphisms may only become apparent in later life.

Keywords: Apolipoprotein E, hippocampal volume, magnetic resonance imaging, young healthy adolescents

INTRODUCTION

The hippocampus has a key role in Alzheimer's disease (AD) and is among one of the first brain regions to show characteristic signs of neurofibrillary tangle pathology, which can be observed pre-symptomatically in adults as young as 20 years [1, 2]. Although hippocampal atrophy is commonly seen in AD, studies have also demonstrated lower hippocampal volumes in healthy older adults and amnestic mild cognitive impairment subjects (MCI) [3–6].

The presence of the apolipoprotein (ApoE) ε4 allele is a major genetic risk factor for the development of late onset AD [7–9], whereas possession of the ε2 allele has been suggested to confer a protective effect against the disease [10, 11]. Healthy adult carriers of the ApoE ε4 allele may be more vulnerable to degeneration of the hippocampus as they enter middle age [12, 13], and show altered patterns of brain activity in response to non-verbal stimuli [14]. A recent study has also demonstrated that homozygous ApoE ε4 carriers (ε4/ε4) may demonstrate wider patterns of cortical atrophy than heterozygous carriers (ε4/no ε4), thus suggesting a possible ε4 allele dose-dependent effect [15]. However, a small number of studies have failed to replicate these findings [12, 16], and others have conversely reported advantageous effects of the ApoE ε4 genotype in young individuals [17].

Less work has addressed the effect of ApoE polymorphisms in healthy children and adolescents, and the core aspects of neuronal development in these individuals are less clear. ApoE ε2 allele carriers stave off the effects of AD [18, 19], but whether properties of the ε2 allele could have a positive effect on neuronal development in adolescence remains largely unexplored. Using a cohort of 1,412 adolescents from the IMAGEN study, we examined the possibility that the ε4 and ε2 alleles may affect hippocampal volume in adolescents, and either render them at risk or protect them from future age-related neurodegeneration.

MATERIALS AND METHOD

Healthy adolescents were studied from the European multi-center neuroimaging-genetics IMAGEN project [20]. A total of 1,412 adolescents had ApoE genotype available.

MR images were acquired using 3T MRI systems from major MR manufacturers (Siemens, Philips, Bruker, and General Electric). A standardized imaging protocol was used to ensure homogeneity in data acquisition across different scanners. The protocol included a high resolution 3D T1-weighted ultrafast gradient echo volume (voxel size $1.1 \times 1.1 \times 1.1\ mm^3$) and axial proton density T2-weighted fast spin echo images based on the ADNI study protocol (http://adni.loni.ucla.edu/). Full details have been previously reported [20]. Quality control was carried out using previously described criteria for scanner related phantom work and to ensure adequate quality control of the T1-weighted volume images such as avoidance of wraparound artefacts and minimal levels of subject motion [20–22]. The Freesurfer analysis pipeline (version 5.1.0) was used to produce left and right hippocampal volumes for each subject. Raw hippocampal volumes and hippocampal volumes normalized by their respective intracranial volumes were determined [23] as detailed in previous publications [24, 25].

Table 1
Demographic and cognitive characteristics of carriers and non-carriers of the APOE ε4 allele

	ApoE ε4 carriers ($n=343$)	ApoE ε4 non-carriers ($n=1069$)	t-value	p	ApoE ε2 carriers ($n=212$)	ApoE ε2 non-carriers ($n=1200$)	t-value	p
Age (years)	14.44 ± 0.40	14.45 ± 0.41	−0.104	0.917	14.41 ± 0.39	14.45 ± 0.41	−1.248	0.212
Gender (Male/Female)	169/174	534/535	–	0.852	114/98	589/611	–	0.233
BMI	20.86 ± 3.27	20.71 ± 3.56	0.673	0.501	20.72 ± 3.26	20.75 ± 3.53	−0.126	0.900
Verbal IQ	111.29 ± 14.84	111.29 ± 15.51	−0.003	0.997	110.26 ± 15.56	111.48 ± 15.31	−1.06	0.289
Performance IQ	107.84 ± 13.93	107.54 ± 14.47	0.336	0.737	106.89 ± 14.58	107.74 ± 14.30	−0.80	0.424
CANTAB SWM strategy	31.10 ± 5.41	31.22 ± 5.42	−0.336	0.737	31.36 ± 5.20	31.16 ± 5.46	0.490	0.367
Normalized R hippocampus*	4351.8 ± 436.9	4305.1 ± 474.4	–	0.289	4332.4 ± 504.9	4313.6 ± 458.8	–	0.103
Normalized L hippocampus*	4226.0 ± 504.1	4224.2 ± 475.3	–	0.406	4232.4 ± 518.2	4234.7 ± 476.3	–	0.357
Raw R hippocampus	4351.8 ± 436.9	4305.1 ± 474.4	–	0.074	4332.4 ± 504.9	4313.6 ± 458.8	–	0.893
Raw L hippocampus	4226.0 ± 504.1	4224.2 ± 475.3	–	0.111	4232.4 ± 518.2	4234.7 ± 476.3	–	0.564

Values represent Mean ± Standard Deviation. A p-value of 0.05 was considered significant for all tests. Continuous variables were inspected using parametric t-tests (t-value) and categorical variables were inspected using fisher exact tests. Hippocampal volume differences were examined using ANCOVA models which co-varied for age, gender, and site ID. *Normalized hippocampal volumes (Hippocampal volume/intracranial volume) were analyzed but raw hippocampal volumes are reported in mm^3. BMI, body mass index; Verbal IQ, verbal intelligence scale; Performance IQ, performance intelligence scale; CANTAB SWM strategy; spatial working memory task score.

Table 2
Dose-dependent effects of ApoE ε4 and ApoE ε2 allelic status on hippocampal volumes

	Right hippocampal volume (mm^3)	p	Left hippocampal volume (mm^3)	p
ApoE ε4 status				
ApoE ε4 allele = 0 ($n=1069$)	4305.0 ± 474.4	0.283	4224.2 ± 475.3	0.399
ApoE ε4 allele = 1 ($n=321$)	4351.2 ± 431.1	–	4226.4 ± 502.1	–
ApoE ε4 allele = 2 ($n=22$)	4360.9 ± 525.7	–	4260.2 ± 545.5	–
ApoE ε2 status				
ApoE ε2 allele = 0 ($n=1200$)	4313.6 ± 458.8	0.132	4234.7 ± 476.3	0.489
ApoE ε2 allele = 1 ($n=199$)	4343.1 ± 512.1	–	4247.0 ± 520.6	–
ApoE ε2 allele = 2 ($n=13$)	4168.4 ± 351.3	–	4008.2 ± 438.6	–

Values represent Mean ± standard deviation. Comparisons were made using ANCOVA, and models were adjusted for age, gender, and site ID.

Blood samples were collected for DNA analysis and extraction from each subject in the study. Samples were subsequently genotyped using the Illumina Quad 610 and 660 arrays (Illumina, San Diego, CA, USA) [20]. Two ApoE single nucleotide polymorphisms, rs429358 (T, C) and rs7412 (C, T), were used to identify 3 allelic variants of ApoE (ε2, ε3, and ε4) in order to define a subject's genotype.

The R statistical software environment, version 2.15.2, was used to perform all statistical analyses. To compare demographic statistics (age, gender, CANTAB SWM strategy scores, verbal and performance IQ), Fisher exact tests and two sample t-tests were conducted. A generalized linear model was used, adjusting for age and gender, to determine hippocampal volume differences between carriers and non-carriers of the ApoE ε4 and ε2 alleles and possible dose-dependent effects of each allele on hippocampal volume. Comparisons of the ApoE ε4 and ε2 alleles were also conducted using a previously described asymmetry index (AI) [26] for the hippocampus and were tested using one-way ANOVA.

RESULTS

Healthy adolescents possessing either the ApoE ε4 or ε2 alleles did not significantly differ in terms of demographics (Table 1). No hippocampal volume differences were observed between carriers and non-carriers of the ApoE ε4 allele (right hippocampus: $F=22.88$, $p=0.289$, left hippocampus: $F=18.9$, $p=0.406$) or the ε2 allele (right hippocampus: $F=23.42$, $p=0.103$, left hippocampus: $F=18.96$, $p=0.357$). These results were consistent when tests were repeated on raw hippocampal volumes (Table 1). No significant differences in the asymmetry index for the hippocampus were observed between ApoE ε4 carriers (AI = 2.23 ± 9.40) and non-carriers (AI = 1.90 ± 10.27) ($p=0.591$) and ApoE ε2 carriers (AI = 2.36 ± 11.01) and non-carriers (AI = 1.92 ± 9.89) ($p=0.547$). Furthermore, no evidence of a dose-dependent effect of ApoE ε4 or ε2 alleles on hippocampal volume and hippocampal asymmetry were established (Table 2). Direct comparisons of memory and IQ performance against both

ε2 and ε4 genotype did not produce any significant results.

DISCUSSION

In this study, a large cohort of young adolescents was used to compare the effects of different ApoE gene polymorphisms on hippocampal volume. Contrary to some recent studies [2, 13], no hippocampal volume differences were observed between carriers and non-carriers of the ApoE ε4 allele, a major genetic risk factor for the development of late-onset AD. Studies that have demonstrated an ApoE ε4 genotypic effect on structural brain phenotypes such as the hippocampus, entorhinal cortex, and other gray matter structures, have generally done so using older non-demented and healthy middle-aged individuals [27–32].

In healthy adults and elderly subjects, a normal asymmetry of the hippocampus exists with the right hippocampus larger than the left [33, 34]. Previous studies have suggested that alteration of asymmetry is associated with the ApoE ε4 genotype [26, 35] and is progressively reduced in AD patients possessing the ε4 allele [36]. In the current study, no differences in hippocampal asymmetry were found between carriers and non-carriers of the ApoE ε4 and ε2 alleles.

The possibility of a gene dose-dependent effect of ApoE ε4 was also investigated. Although the neuroanatomic effects of ApoE ε4 have been extensively studied [15, 37, 38], even less is known about the deleterious effects associated with the presence of two ε4 alleles in children and adolescents. However, direct comparisons of ε4 allele dosages in our cohort showed no differences in subject's hippocampal volumes, despite a previous study suggesting a linearly proportional rate of hippocampal atrophy to allele load [39].

One possible explanation for our findings are that ApoE ε4 genotype exerts a quiescent effect on the hippocampus, and as a result, neuroanatomic effects of the ε4 allele in this region may lie dormant in young adolescents and gradually become more salient in earlier adulthood. Evidence of this gradual effect can be seen in studies that observe early structural changes in volumes of gray matter [2, 40], as well as differences in white matter integrity [41, 42] among ε4 carriers aged 21 and above.

Prior studies comparing the effects of ApoE polymorphisms on brain imaging phenotypes have yielded equivocal findings; with some presenting no evidence of an ε4 genotypic effect on gray matter volumes [3, 43, 44], and others suggesting an antagonistic pleiotropic effect of the gene during neuronal development [45, 46]. Although a definitive conclusion has not been drawn, this could be due to differences in sample size, image pre-processing methods, and a lack of sample diversity or ethnic homogeneity.

Structural MRI studies have examined perinatal brain development in infants [47, 48] with ApoE ε4 found to predict reduced temporal cortex volumes. A confound of this study was that subjects were enriched for parents with psychiatric conditions, several of which are characterized by reduced hippocampal volume. Although such studies provide a better understanding of the perinatal effects associated with brain development, adolescence is also a period in which neurobiological changes may influence asynchronous brain maturation [49, 50].

Regional differences in hippocampal volume between ApoE ε2 carriers and non-carriers were not found. Hence no evidence of a ε2 protective effect was established. The putative protective effect of ApoE ε2 remains a matter of debate and has generated contradictory findings. Some volumetric MRI studies do not support a disease staving protective effect in healthy older subjects [51, 52], however, postmortem examinations have shown less AD-related neuropathological changes in ε2 carriers relative to ε3 homozygotes [53]. Only one study [19] was able to establish a protective effect of the ε2 variant.

Direct comparisons of memory and IQ performance against the ε4 genotype also did not produce any significant results. However, as only a single test of cognition from the CANTAB battery was assessed, we cannot definitively exclude the possibility of a ε4 genotypic effect on cognitive function. Nevertheless, the finding that ApoE ε4 allelic status does not relate to intelligence and cognitive function fits with previous studies reporting little or no effect of the ε4 allele on working memory and intellectual capacity [54, 55].

In summary, this study suggests that hippocampal volume differences associated with ApoE ε4 and ε2 are not evident in 14-year olds, and that neuroanatomic effects of these variants may only become apparent later in life.

ACKNOWLEDGMENTS

Support for this study was provided by the IMAGEN project, which receives research funding from the European Community's Sixth Framework Program (LSHM-CT-2007-037286) and coordinated project

ADAMS (242257), as well as the NIHR Biomedical Research Centre for Mental Health and NIHR Biomedical Research Unit for Dementia at South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, King's College London, Alzheimer Research UK and the IMI funded European Medical Information Framework. GJB received honoraria for teaching during the course of this study and receives consultancy payments from IXICO.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=2007).

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